REMARKS/ARGUMENTS

Status of the Claims

Claims 12-19 were rejected. Claims 1-11 were previously cancelled without prejudice or disclaimer. Applicants reserve the right to pursue these claims in a continuation or divisional application. Claims 12-19 are pending in the present application.

The Rejection of the Claims Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 12-16, 18, and 19 were rejected under 35 U.S.C. § 102(b) as being anticipated by Nho *et al.* (U.S. Patent No. 5,234,903) and Davis *et al.* (U.S. Patent No. 4,179,337), which is incorporated by reference in its entirety into Nho *et al.* This rejection is respectfully traversed.

Claims 12-19 are drawn to a method of preparing a chemically modified hemoglobin solution that is substantially free of contaminants comprising dissolving an activated PEG in a solvent in which it is stable, filtering the activated PEG solution to substantially reduce the level of contaminants, and combining the filtered activated PEG solution with a hemoglobin solution. Thus, the claimed methods require that the activated PEG must first be dissolved in an appropriate solvent and then filtered before using the activated PEG solution to chemically modify hemoglobin. A critical element of the claimed invention is the use of a filtered activated PEG solution to chemically modify hemoglobin. As noted in the Response to the Final Office Action filed February 15, 2005, while contaminants such as endotoxin can be removed after PEGylation, purification following chemical modification of the hemoglobin solution results in undesirable changes to the protein composition (e.g., removal of antioxidant enzymes associated with the PHP complex) or even in destruction of the product (page 3, lines 1-3). Therefore, the use of a stable, filtered activated PEG solution is critical to the production of a final hemoglobin product that is substantially free of contaminants.

Contrary to the Examiner's assertions, a *prima facie* case of anticipation under 35 U.S.C. § 102 has not been established. According to the Federal Circuit, "anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration." *W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). Nho *et al.* teach a method for producing a chemically modified hemoglobin solution comprising modifying

a deoxygenated and reduced hemoglobin solution with an activated PEG, *followed* by filtration and sterilization of the modified hemoglobin solution to remove contaminants (e.g., endotoxin). In contrast to the claimed methods, the cited reference does not teach first dissolving the activated PEG in a solvent in which it is stable and then filtering the activated PEG solution to substantially reduce contaminant levels *prior* to combining it with the hemoglobin solution. In fact, the cited reference teaches that the activated PEG is added to the hemoglobin fraction as a powder, not as a solution as required by the present claims. Moreover, given that many activated PEGs are labile in water and, as a result, prior to the present invention activated PEGs were typically added to hemoglobin solutions in a powdered form, the claim limitation at issue is also not inherently disclosed by the cited reference. Nho *et al.* do not teach or suggest preparing a filtered activated PEG solution and using the filtered solution to modify hemoglobin. The reference does not teach each and every element of the claims and, therefore, does not anticipate the present invention.

The Examiner maintains, however, that Nho *et al.* do teach the claimed methods, including the steps of dissolving an activated PEG in solution and filtering the activated PEG solution to substantially reduce contaminants. In the Response to the Final Office Action filed February 15, 2005, Applicants previously explained in detail that the filtration steps taught by Nho *et al.*, particularly at column 14, are performed during the synthesis of an activated PEG powder and are not equivalent to preparing and filtering an activated PEG solution to substantially reduce contaminants. The Examiner rejected these arguments, stating that "Nho's methods...are not limited to those described in column 14" and that the reference "taught...that '[a]ny method known in the art may be used to activate the polyalkylene oxide for subsequent conjugation to a hemoglobin'" (page 4, lines 6-10, Office Action mailed March 11, 2005). This reasoning is insufficient to establish a *prima facie* case of anticipation because the required steps of dissolving an activated PEG in a solvent in which the activated PEG is stable, filtering the activated PEG solution to substantially reduce contaminant levels, and combining the filtered activated PEG solution with a hemoglobin solution are not taught or suggested by the cited reference. The mere statement that "any method" may be used to activate a PEG is not equivalent to teaching the preparation and filtration of an activated PEG solution. Furthermore,

it is clear throughout the Nho *et al.* patent that the Applicants only contemplated the preparation of a powdered activated PEG and the use of this solid activated PEG to chemically modify hemoglobin (see, for example, column 14, lines 22-25 and lines 38-39). Nho *et al.* simply do not teach or suggest preparing a stable activated PEG solution that is substantially free of contaminants.

The Examiner further cites Davis *et al.*, which is incorporated by reference into the Nho *et al.* patent, to argue that the claimed steps of dissolving an activated PEG in a solvent in which it is stable and filtering the activated PEG solution to substantially reduce contaminants are disclosed by Nho *et al.* Specifically, the Examiner directs Applicants' attention to Example VIII, which the Examiner maintains teaches the preparation and subsequent filtration of an activated PEG solution. Applicants respectfully disagree with the Examiner's analysis of Example VIII and the Davis *et al.* reference generally.

Example VIII of the Davis *et al.* patent is directed to the preparation of an activated PEG (i.e., ω-amino PEG) for use in chemically modifying proteins. The synthesis of the activated ω-amino PEG requires several reaction steps during which intermediate PEG products are synthesized. These intermediate reaction products are <u>not</u> activated PEGs. The first step in the synthesis of the activated PEG involves dissolving the unactivated PEG in toluene and distilling the toluene from the mixture to remove traces of moisture. The solution is then cooled, and anhydrous triethylamine and p-toluene sulfonyl chloride are added. The solution is kept overnight at room temperature and filtered. The filtrate is cooled, and the precipitate is collected. The collected polymer is dissolved in absolute ethanol along with sodium azide, and the solution boiled under reflux to yield the intermediate PEG product ω-azido PEG. The ethanol solution of the intermediate ω-azido PEG is hydrogenated, filtered, and concentrated. After the addition of dry ether, the polymer is collected by filtration. The resultant polymer is a <u>solid</u>, activated PEG, specifically ω-amino PEG, that is then used to chemically modify a protein of interest. See generally column 11, lines 50-68 and column 12, lines 1-11.

The Examiner maintains that the ethanol solution of ω-azido PEG described above is "the activated PEG [that] was used in the PEGylation process" (page 4, line 20, Office Action mailed March 11, 2005). This assertion is incorrect. The ethanol solution of ω-azido PEG is <u>not</u> the

activated PEG; rather, it is an intermediate PEG product synthesized during the process for preparing the activated ω-amino PEG. Thus, the fact that the ethanol solution of the intermediate ω-azido PEG is filtered through some undisclosed filter is irrelevant here because the claims require that the activated PEG is dissolved in a solvent in which it is stable and that the activated PEG solution is filtered prior to combining it with a hemoglobin solution. Davis *et al.* do not teach or suggest dissolving the activated ω-amino PEG in a solvent in which it is stable and filtering the activated PEG solution to substantially reduce contaminants.

The Examiner further discusses the filtration of the ethanol solution of the intermediate ω-azido PEG taught by Davis *et al.*, stating that "Davis' filtration step is expected to 'substantially reduce' the levels of any generic 'contaminants' or specifically 'endotoxin contaminant levels'" and that "it is well known in the art that such a filtration process does remove contaminants, irrespective of whether they are unreacted reactants or regents [sic], bacterial contaminants or endotoxin contaminants" (page 5, lines 2-5, Office Action mailed March 11, 2005). Example VIII, however, only states that the ethanolic solution of ω-azido PEG is "filtered" (column 12, line 8). A person skilled in the art of preparing activated PEGs would interpret this step as involving minimal filtration to remove insoluble material through a sintered glass filter or a paper filter. See, for example, Abuchowski *et al.* (1984) Cancer Biochem. Biophys. 7:175-186, which was cited by Nho *et al.* at column 13, lines 29-31. While Applicants maintain that the filtration of the ethanol solution of the intermediate ω-azido PEG is not described in sufficient detail to permit the Examiner to draw the above conclusions regarding the degree of purification obtained, the details of the filtration are immaterial because the Davis *et al.* patent *does not teach filtration of an activated PEG solution, as required by the claimed methods*. The filtration of the intermediate PEG solution taught by Davis *et al.* is not equivalent to filtration of an activated PEG solution. In fact, Davis *et al.* do not teach or suggest dissolving an activated PEG in a solvent and filtering the activated PEG solution through a filter of any size anywhere in the description or in any of the experimental examples. Thus, the cited references do not teach each and every element of the claims and, therefore, are not anticipatory.

The Examiner further asserts that "the burden is on Applicants to show a novel or an unobvious difference between the instant invention and the prior art invention, i.e., to show that

the prior art filtering step does not result in the same substantial reduction in the levels of contaminants" in the activated PEG as that recited in the present claims (page 5, lines 13-16, Office Action mailed March 11, 2005). The Examiner cites case law to support this assertion. *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980). In the cases referenced by the Examiner, however, the prior art expressly disclosed all of the claimed method steps but did not include a functional limitation recited in the claims. *In re Best*, 195 USPQ at 432. Under those facts, the Court held that the Patent Office has the authority to require the Applicant to prove that the prior art does not possess the functional limitation where there is reason to believe that the functional limitation may be an *inherent* characteristic of the prior art. *Id.* at 433 (citing *In re Swinehart*, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). The present case is distinguishable from the cited case law. Here, the references do not teach all of the required steps of the present claims, and, therefore, the issue is not whether a functional limitation (i.e., the level of reduction in contaminants) is inherently disclosed by the prior art. As discussed above, the prior art cited by the Examiner simply does not teach dissolving an activated PEG in a solvent and filtering the activated PEG solution to substantially reduce contaminants. Thus, contrary to the Examiner's conclusion, the cited case law is inapplicable to the present facts, and the burden remains on the Examiner to present a *prima facie* case of anticipation by establishing that a single prior art reference teaches each and every element of the claimed invention. Because neither Nho *et al.* nor the incorporated Davis *et al.* reference teaches filtering an activated PEG solution and using the filtered activated PEG solution to modify hemoglobin, the Examiner has failed to establish a *prima facie* case of anticipation.

The Examiner also concludes that the cited references specifically anticipate claim 14, which further requires that the activated PEG is dissolved in a solvent selected from the group consisting of ethanol, methanol, and acetonitrile. The Examiner bases this conclusion on the fact that Davis *et al.* disclose an ethanol solution of ω-azido PEG. Again, the Examiner is incorrectly equating an ethanol solution of the unactivated ω-azido PEG with an activated PEG solution. Davis *et al.* teach preparing and filtering an ethanol solution containing an unactivated, intermediate PEG but do not disclose dissolving an activated PEG in ethanol, methanol, or

acetonitrile, as recited in claim 14. Therefore, claim 14 is not anticipated by Nho *et al.*/Davis *et al.*

In summary, the claimed methods require that the activated PEG is dissolved in a solvent in which it is stable, that the activated PEG solution is filtered to substantially reduce the level of contaminants, and that the resulting filtered activated PEG solution is combined with a hemoglobin solution. Preparing and filtering a stable activated PEG solution and then using the filtered solution to modify hemoglobin are critical steps in the present methods for producing a hemoglobin solution that is substantially free of contaminants. Moreover, *prior to the present disclosure it was not known that a stable activated PEG solution could be produced, filtered to substantially reduce contaminant levels, and successfully used to modify a hemoglobin solution.* Nho *et al.* teach synthesizing an activated PEG powder, combining the solid activated PEG with hemoglobin, and filtering the hemoglobin solution *after* chemical modification to remove endotoxin and other contaminants from the final product. The Davis *et al.* patent, incorporated by reference into Nho *et al.*, discloses preparing an ethanol solution containing an intermediate PEG and filtering this solution through an unspecified filter as part of the synthesis of the final, activated PEG. The activated PEGs of Davis *et al.* are not dissolved in a solvent and filtered through a filter of any size. Therefore, Nho *et al.* and Davis *et al.* do not teach the critical steps of preparing a stable activated PEG solution and filtering the activated PEG solution to substantially reduce contaminant levels prior to combining the filtered solution with hemoglobin. Accordingly, the references do not teach each and every element of the claims, and anticipation under 35 U.S.C. § 102 has not been established. Applicants respectfully request that the rejection of claims 12-16, 18, and 19 be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claim 17 was rejected under 35 U.S.C. § 103 as being unpatentable over Nho *et al.* This rejection is respectfully traversed.

Dependent claim 17 further comprises filtering the activated PEG solution through a 0.2 micron nylon filter. Nho *et al.* teach using a 0.2 micron Zetapor® nylon filter to sterilize the final chemically modified hemoglobin solution to render it substantially endotoxin-free. In light

of this, the Examiner maintains that it would have been obvious to one of skill in the art to use a 0.2 micron nylon filter to filter an activated PEG solution to substantially reduce contaminant levels. As indicated above, Nho *et al.*, even in view of the incorporated disclosure of Davis *et al.*, do not teach or suggest dissolving an activated PEG in a solvent, filtering the activated PEG solution through a filter of any size, and using the filtered activated PEG solution to modify a hemoglobin solution. In fact, the activated PEG used by Nho *et al.* is a powder, not a solution and, therefore, is not filtered. Furthermore, the incorporated Davis *et al.* reference teaches only the filtration of a solution containing an intermediate, unactivated PEG through an undisclosed filter, not the filtration of an activated PEG solution, as recited in the present claims. And finally, the mere fact that Nho *et al.* use a 0.2 micron nylon filter to remove contaminants from a chemically modified hemoglobin solution is no indication that one of skill in the art would have been motivated to dissolve an activated PEG in a solvent in which it is stable, filter the activated PEG solution through a filter of any size, and then combine the filtered activated PEG solution with a hemoglobin solution. Accordingly, the invention of claim 17 is not obvious.

For the reasons presented above, the Examiner has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully submit that the claimed methods for producing a chemically modified hemoglobin solution that is substantially free of contaminants are not obvious in view of the cited references and request that the rejection of claim 17 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

The Examiner is respectfully requested to withdraw the rejections and allow claims 12-19. In any event, the Examiner is respectfully requested to consider the above remarks for the purposes of further prosecution.

Accordingly, in view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Appl. No.: 09/934,300
Amdt. dated 06/13/2005
Reply to Office action of March 11, 2005

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Michelle L. Cunningham
Registration No. 51,072

Customer No. 29122
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to the U.S. Patent and Trademark Office Fax No. (703) 872-9306 on the date shown below.

Pamela Lockley — June 13, 2005
Pamela Lockley — Date

RTA01/2182133v1